REMARKS / ARGUMENTS

Upon entry of the present amendments, new claims 35-37 are pending in the application. Claims 1-29 and 31-34 are withdrawn from consideration. Claim 30 is cancelled without prejudice. New claims 35-37 have been added. Support for new claim 35 appears at least in original claim 1 and claim 3 as well as at page 4, lines 21-30 through page 5, lines 1-13 and page 19, line 10 of the specification as originally filed. Support for new claim 36 appears at least at page 27, lines 11-30 and page 29, lines 6-31 in the specification as originally filed. Support for new claim 37 appears at least at page 27, lines 11-30 through page 28, lines 1-4 in the specification as originally filed. The bases for the Examiner's rejection of claim 30 (now cancelled) directed to a method for by-passing cell drug resistance is addressed below as new claims 35-37 are also directed to a similar method. The foregoing amendments were made without any intention to abandon any subject matter, but with the intention that one or more claims of the same, lesser, or greater scope may be pursued in a later application or in a continuation, continuation-in-part, or divisional application. The present amendment does not add new matter.

Specification

The Applicants have attended to the Examiner's objections regarding informalities in accordance with the Examiner's suggestions. Specifically, page 1 has been amended to reflect the priority status of the present application. Page 16, line 32 has been amended so the section title reflects the appropriate language.

Claim objections

Claim 30 has been cancelled and new claim 35 is presented herein. Claim 35 corresponds in scope to former claim 30, rewritten to be independent. New claims 36-37 have been introduced to protect specific embodiments. The expression "target cell" has been replaced with "tumor cell" to be consistent throughout the claim.

Claim Rejections -35 U.S.C. § 112, second paragraph

The Examiner rejected claim 30 pursuant to 35 U.S.C. §112, second paragraph as indefinite for failing to particularly point out and distinctly claim the subject matter the Applicants regard as their invention. Specifically, the phrase "by-passing resistance" in claim 30 is alleged by the Examiner to be indefinite for the three following reasons: a) it cannot be determined how

the compound is by-passing resistance of tumor cells by p-glycoprotein pump: is it by-passing resistance of tumor cells by using a PGP or by-passing resistance of tumor cells mediated by PGP; b) it cannot be determined whether the tumor cells are "resistant" or "sensitive"; and c) it cannot be determined whether "a patient in need of such treatment" relates to a person in need of a treatment that requires by-passing or is a by-passing treatment.

Claim 30 has been cancelled and new claims 35-37 have been introduced to point out and distinctly claim the subject matter of the invention. The Examiner's rejection pursuant to 35 U.S.C. §112, second paragraph is mooted by the cancellation of claim 30. The Applicants believe, however, that claims 35-37 are in condition for allowance as they fully comply with the requirements of 35 U.S.C. §112, second paragraph. The purpose of the method, *i.e.*, "for by-passing tumor cell drug resistance mediated by p-glycoprotein pump (PGP)" has been clarified. The tumor cells as defined in the claims are resistant to drugs. The aim of the claimed method is to treat these cells. Support for defining W as a targeting agent can be found throughout the specification and more specifically on page 19, line 10.

Claim Rejections -35 U.S.C. § 112, first paragraph

The Examiner rejected claim 30 pursuant to 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. The Examiner alleges that claim 30 contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the Applicants, at the time the application was filed, had possession of the claimed invention. Claim 30 has been cancelled and new claims 35-37 are pending. The Examiner's rejection pursuant to 35 U.S.C. §112, first paragraph is mooted by the cancellation of claim 30. The Applicants believe, however, that claims 35-37 are in condition for allowance as they fully comply with the requirements of 35 U.S.C. §112, first paragraph.

The Applicants assert that limiting the chemotherapeutic agent X to doxorubicin would be unduly restrictive and unfair to the Applicants, as the specification did have examples for other chemotherapeutic agents such as paclitaxel. Figures 5 to 7 illustrate the use of paclitaxel. More specifically, Fig. 7 illustrates that paclitaxel-MC192 is efficient at reducing tumor growth and at increasing survival *in vivo*. Furthermore, in view of these examples, the person skilled in the art would have no hesitation replacing doxorubicin with other chemotherapeutic agents that could be coupled to a compound defined in new claim 35.

Limiting the ligand W to a specific monoclonal antibody such as a-IR3 mAb would be unduly restrictive and unfair to the Applicants. The specification did have examples for other

mAbs. In the application, other mAbs, such as MC192 (p75 binding), 5C3 (TrkA binding) are described on pages 6, 11, 26 and 27 and figures 4 to 7 of the application. Furthermore, the application describes a compound in accordance with a preferred embodiment of the present invention, wherein when W is a primary biologically active molecule indirectly binding to the target cell, the compound further comprises W' which is a secondary biologically active molecule selectively binding to W and adapted to selectively bind the target cell. the application describes a compound in accordance with another embodiment of the present invention, wherein the primary and/or the secondary biologically active molecules is an antibody. The application describes a compound in accordance with another embodiment of the present invention, wherein a primary antibody is of a species and a secondary antibody is of a different species. The application describes a compound in accordance with another embodiment of the present invention, wherein the secondary biologically active molecule is a rabbit-antimouse antibody. Support for these embodiments can be found throughout the specification and more specifically on page 6.

Other embodiments add to the teaching of the invention. They include an "all purpose "secondary reagent antibody, that can be used to target ANY receptor indirectly by way of binding to a primary antibody targeting any receptor. Small peptidomimetic ligand of the HER2 receptor as ligands (W) coupled to Taxol can be used. These results were obtained from the teaching of the present invention and are reported in the enclosed references: DNA and Cell Biology, Vol. 24, No.6, 2005, pp.350-358, Guillemard *et al.* (Exhibit A); Cancer Research 61, 694-699, January 15, 2001, Guillemard *et al.* (Exhibit B)

Claim Rejections -35 U.S.C. § 102

The Examiner rejected claim 30 under 35 U.S.C. §102(b) as allegedly anticipated by Kopecek *et al.*, U.S. Pat. No. 5,258,453 (1993). Claim 30 has been cancelled and new claims 35-37 are pending. The Examiner's rejection pursuant to 35 U.S.C. §102(b) is mooted by the cancellation of claim 30. The Applicants believe, however, that claims 35-37 are in condition for allowance as they are not anticipated by Kopecek *et al.* (US 5,258,453).

Kopecek *et al.* (US 5,258,453) does not pertain to Multi Drug Resistance (MDR). The only statements (with no data to support it in the specification) regarding MDR are the following:

On page 1, lines 51-54:

> "The present invention minimizes the amount of cancer cells which are resistant to chemotherapy, thus decreasing substantially the possibility of tumor recurrence."

The statement indicates that their invention is better suited to kill tumor cells, thus decreasing substantially the possibility of tumor cells recurring in a drug resistant state after drug treatment. This is the concept of drug selection pressure. The present invention is different in that the treatment bypasses the PGP causing resistance of tumor cells.

On page 1, lines 54-59:

> "This approach has a higher potential in the successful treatment of multidrug resistant cells (MDR) than the presently available therapies. The concentration of drugs in the cell, when this method is used, is increased, even if the transport of the drugs into the cell interior or MDR cells is impaired."

The present invention is not claiming a method that bypasses impaired drug transport into the interior of tumor cells expressing MDR . Moreover, the tumor cells tested in the Kopecek patent are not MDR overexpressing.

The authors in Kopecek et al go further to discard targeted delivery into cells and bypassing MDR (the core of the present invention) with the following statement on page 1, line 65 to page 2, line 2:

> "The polymeric drug will bind to the cell surface receptor/antigen) (sic) of MDR cells and may not be internalized. However, after irradiation, the photoactivatable drug will produce singlet oxygen with consequent membrane damage, ultimately resulting in cell death." (emphasis added)

The Applicants point out that it is not possible that a drug can bypass MDR pumps if it is not internalized.

On page 8, lines 5-12:

> "An anticancer drug enhances PDT treatment (and vice versa) because long term cure of solid tumors is difficult to achieve with PDT. On the other hand, chemotherapeutic agents have their own share of problems including multidrug resistance and other toxic side effects. The present invention reduces side effects because lower doses of copolymers are required. "

This statement clearly and unequivocally indicates that there is nothing relating to bypassing MDR pumps. It is simply that the Kopecek patent claims that lower drug doses kill more efficiently, thus reducing side effects and potentially avoiding the tumors from evolving

towards drug resistance. The avoidance of drug resistance is not related at all with their invention bypassing MDR but simply with preventing tumors from being selected towards drug resistance because potentially there are less tumor cells surviving their treatment.

In order to better distinguish the invention, Claim 35 has been amended to specify that the breakable linker is cleavable in the cell. In Kopecek, the linker is broken outside the cells with light. In view of the above, it is respectfully submitted that Kopecek does not anticipate nor remotely suggest the present invention as now claimed.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submits that the pending claims are in condition for allowance and respectfully request the same. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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APPENDIX